UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,280	09/26/2003	Gregory Alan Lazar	A-71386-7	8317

7590 07/26/2006

Robin M. Silva, Esq.
Dorsey & Whitney LLP
Intellectual Property Department
Four Embarcadero Center, Suite 3400
San Francisco, CA 94111-4187

EXAMINER
CROWDER, CHUN

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/672,280	LAZAR ET AL.	
	Examiner	Art Unit	
	Chun Crowder	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55, 57-59, 61-85* is/are pending in the application.

4a) Of the above claim(s) *4,5,8,9,16,17,28-33,41,42,44-55,57,58,61,62, 64-85* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6, 7, 10-15, 18-27, 34-40, 43, 59, and 63,* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I, and species of an antibody, IgG1, targeting CD20, 239D substitution, increased affinity for FcγR and no carbohydrate modification, filed 05/24/2006, is acknowledged.

Claims 56 and 60 have been canceled.

Claims 1-55, 57-59, and 61-85 are pending.

Claims 4, 5, 8, 9, 16, 17, 28, 29, 30-33, 41, 42, 44-55, 57-58, 61, 62, and 64-85 have been withdrawn from further consideration by the Examiner, under 37 C.F.R. 1.142(b), as being drawn to nonelected inventions.

Claims 1-3, 6, 7, 10-15, 18-27, 34-40, 43, 59, and 63, read on an antibody, IgG1, targeting CD20, 239D substitution, increased affinity for FcγR and no carbohydrate modification, are currently under consideration.

2. The instant application appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

3. Applicant's claim for domestic priority under 35 U.S.C. 119 (e) is acknowledged. However, the provisional applications USSNs 60/414,433 and 60/442,301 upon which priority is claimed fail to provide adequate support under 35 U.S.C. 112 for claims 3, 6, 7, 14, 15, 26, 27, 39, 40, 43, and 63 of this application. Specifically, insufficient support was identified for the limitation of "position.... 239". Consequently, the claims have been accorded the priority of the filing date of the priority applications USSNs 60/467,606 (05/02/2003) and 60/477,839 (06/12/2003).

Should applicant disagree with the Examiner's factual determination above, it is incumbent upon applicant to provide a showing that specifically supports the instant claim limitations.

4. Applicant's IDS, filed 05/17/2006, is acknowledged and have been considered except References B20 (WO 00/61739), B21 (WO 01/29246), B27 (WO 02/30954), and B28 (WO 02/31140) for which have only been considered to the extent of the English translation of the Abstracts.

5. The application is required to be reviewed and all spelling, TRADEMARK, and like error corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent application, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction is required.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 3, 6, 7, 10-13, 18-27, 34, 35, 43, and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1, 3, 6, 7, 10, 11, 18-27, 34, 35, and 59 are indefinite in its recitation of "modulate" because it is ambiguous as to the direction (positive or negative) or degree of the effect of the said "modulate". The term "modulate" is not defined by the claims, the specification does not provide a standard form ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

B) Claim 34 is indefinite in the recitation of "effector functions" because the metes and bounds of the effector functions is not clear and ambiguous. For example, page 25 of the instant specification discloses certain "effector function" include antibody dependent cell-medialted cytotoxicity (ADCC), antibody dependent cell-mediated phagocytosis (ADCP). However, it is unclear as to which "effector function" or the requisite structural/functional characteristic is/are intended or encompassed by the claimed polypeptide. It is suggested to amend the claim to recite the "effector functions" encompassed by the claimed binding agent. See claim 36 and/or page 25 of the specification for example.

C) Claims 6, 12, 13, 18, and 43 are indefinite in the recitation of "substantially human" and/or "substantially mouse, substantially rat or substantially monkey" because the metes and bounds of the claims is unclear and ambiguous. The phrase is not defined by the claims, the specification does not provide standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

D) Claims 23-27 are indefinite in the recitation of "FcγRIIIa-fold: FcγRIIb-fold ratio" because the phrase fails to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear as to what "FcγRIIIa-fold: FcγRIIb-fold ratio" is intended or encompassed by the claimed polypeptide. The phrase is not defined by the claims, the specification does not provide standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

E) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-3, 6, 7, 10-15, 18-27, 34-40, 43, and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-3, 6, 7, 10-15, 18-27, 34-40, 43, and 59 recite "a polypeptide comprising an Fc variant" as part of the invention.

The specification discloses on pages 27-29 that a "a polypeptide comprising an Fc variant" according to the definition of a variant polypeptide meant an Fc sequence that differs from a parent Fc sequence by at least one amino acid modification, e.g. from about one to about ten amino acid modification, or possess at least 80% homology with a parent polypeptide sequence.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficient enabling description of the claimed invention. The disclosure appears to show only antibodies with certain specified amino acid substitutions. For example, the specification discloses engineered antibodies such as rituximab, alemtuzumab, and trastuzumab with amino acid substitutions in the Fc region (see Example 2 on pages 128-130 of the specification as-filed). The instant claims encompass in their breadth *any* "a polypeptide comprising an Fc variant" comprising with at least one amino acid substitution.

However, there does not appear to be sufficient guidance in the specification as field as to how the skilled artisan would make and use the claimed "variant Fc". The state of the art at the time the invention was made recognized that even single amino acid differences can result in drastically altered function of antibodies. For example, Lund et al. (The Journal of Immunology 1996, 157:4963-4969. Reference C10 on IDS) show that even a single amino acid replacement within the CH2 domain of IgG can alter the glycosylation profile of an antibody therefore influence its effector functions of Fc receptor binding and complement activation (see entire document, particularly Discussion on pages 4966-4968). Further, Lazar et al. (WO 03/074679) teach that the determinants of antibody properties, such as stability, solubility and affinity for antigen, important to its functions are overlapping; thus engineering an antibody to be more soluble may cause a loss in affinity for its antigen (see entire document, particularly page 3).

Given the extensive variation permitted by the instant claim language, the skilled artisan would not reasonably predict such "a polypeptide comprising an Fc variant" to have the same function as the instant claimed invention.

Reasonable correlation must exist between the scope of the claims and scope to enablement set forth. Applicant does not appear to provide guidance as to other "a polypeptide comprising an Fc variant" which meets the claimed limitation of exhibits altered binding to an FcγR.

In addition, it is unpredictable if functional activity will be shared by two polypeptides having 80% identity over the full length of their sequences. The specification does not appear to provide sufficient guidance as to which residues should or should not be changed to preserve any particular function. Although the specification does provide working examples of antibodies such as antibodies with specific position(s) in the Fc region altered (e.g. see Figure 11-13), the variation permitted by the instant claim language is extensive.

However, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the claimed "a polypeptide comprising an Fc variant". The specification provides no direction or guidance regarding how to produce "a polypeptide comprising an Fc variant" as broadly defined by the claims.

In view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Applicant is invited to consider amending the claimed Fc variant/polypeptide to antibody and/or Immunoadhesin as disclosed on pages 22-26 of the instant specification to obviate this rejection.

10. Claims 1-3, 6, 7, 10-15, 18-27, 34-40, 43, and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The following *written description* rejection is set forth herein.

Claims 1-3, 6, 7, 10-15, 18-27, 34-40, 43, and 59 recite "a polypeptide comprising an Fc variant" as part of the invention.

There is insufficient written description in the specification as-filed of "a polypeptide comprising an Fc variant" as recited in the instant claims.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. (See Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, especially page 1106 3rd column). A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. MPEP 2163 II.A.3a.ii.

The claims recite a genus "a polypeptide comprising an Fc variant" as part of the invention without providing a physical structure or testable functional activity for the "a polypeptide comprising an Fc variant".

The genus of the "a polypeptide comprising an Fc variant" are therefore very large. Applicant has disclosed only antibodies with certain amino acid modifications at the Fc region (e.g. see Example 2 on pages 128-130). Thus Applicant has disclosed only a limited species of the "a polypeptide comprising an Fc variant", namely antibodies. The claimed "a polypeptide comprising an Fc variant" lack a common structure essential for their function and the claims do not require any particular structure basis or testable functions be shared by the instant "a polypeptide comprising an Fc variant".

Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required.

It is well known in the art that effector functions such as ADCC is a process where the Fcγ receptors of the natural killer cells and other leukocytes bind to antibody-coated target cells and destroy them (Burton et al. Human antibody effector function. Advances in Immunology, 1992, 51:1-84. See entire document, particularly Figure 18). The antibodies mediating ADCC must have Fc region for binding of Fc receptors as well as regions for binding of target cells.

It does not appear based upon the limited disclosure of antibodies alone that Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the limited number of species disclosed and the extensive variation permitted within the genus of "a polypeptide comprising an Fc variant".

"Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d, 1398, (Fed. Cir. 1997).

The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406.

In the absence of disclosure of relevant, identifying characteristics of the "a polypeptide comprising an Fc variant", there is insufficient written disclosure under 35 U.S.C. 112, first paragraph.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 1115).

Applicant is invited to consider amending the claimed Fc variant/polypeptide to antibody and/or immunoadhesin as disclosed on pages 22-26 of the instant specification to obviate this rejection.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1-3, 6, 7, 10-15, 18-27, 34-40, 43, 59, and 63 are rejected under 35 U.S.C. 102(b) as being anticipated by Presta (WO 00/42072. Reference B1 on IDS) (See entire document).

Presta teaches polypeptide comprising a variant Fc region such as antibody and immunoadhesin. Specifically, Presta teach that the Fc regions of an antibody and immunoadhesin can be modified by amino acid substitutions at positions such as 239 for altered binding affinity to FcγRs (see entire document, particularly Summary of the Invention on pages 5-8). Further, Presta teaches that the Fc region can be human IgG1 and the amino acid substitution can be replacement of any naturally occurring amino acid residues e.g. Asp (D) (e.g. see pages 14-15). Furthermore, Presta teaches that the antibody can be produced using CD20 as antigen and can be further formulated in a pharmaceutical composition (see pages 35-54, in particular).

Given the reference antibody variant comprises amino acid substitution at the same position (position 239) as the claimed polypeptide variant comprising an Fc variant, the claimed functional limitations associated with the polypeptide variant would be inherent properties of the reference antibody.

Therefore, the reference teachings anticipate the claimed invention.

13. Claims 1-3, 6, 7, 10-15, 18-27, 34-40, 43, 59, and 63 are rejected under 35 U.S.C. 102(e) as being anticipated by Presta (US Patent 6,737,056. Reference A97 on IDS) (see entire document).

Presta teaches and claims polypeptide variant e.g. IgG1 with altered effector function comprising amino acid substitutions at positions including 239 (see entire document, particularly Detailed Description of the Preferred Embodiments on columns 9-47 and claims 1-14). Further, Presta teaches that the Fc region can be human IgG1 and the amino acid substitution can be replacement of any naturally occurring amino acid residues e.g. Asp (D) (e.g. see column 12). Furthermore, Presta teaches that the antibody can be produced using CD20 as antigen and can be further formulated in a pharmaceutical composition (e.g. see columns 29-44).

Given the reference antibody variant comprises amino acid substitution at the same position (position 239) as the claimed polypeptide variant comprising an Fc variant, the claimed functional limitations associated with the polypeptide variant would be inherent properties of the reference antibody.

Therefore, the reference teachings anticipate the claimed invention.

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1-3, 6, 7, 10-15, 18-27, 34-40, 43, 59, and 63 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over:

Claims 38-43 45 and 46 of copending USSN 11/483,378,
Claims 38, 40, and 49-57 of copending USSN 11/483,250,
Claims 1-42 of copending USSN 10/822,231,
Claims 1-12 of copending USSN 11/124,620, and
Claims 1-19 of the copending USSN 11/396,495.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant and the copending application claims are drawn to same or nearly the same polypeptide variants with the same modifications to the Fc region at position 239 for altered affinity for FcγRs and effector functions. Given polypeptide variants rely on the same amino acid modification, the instant claims and the conflicting claims would anticipate or render obvious of one another. It is further noted that the instant claims 1, 2, 10-13, 18-25, 34-38, and 59 recite a genus of polypeptide variants comprising Fc variants with at least one amino acid modification without reciting specific amino acid residues. In turn, the species recited in copending claims would thus anticipate the genus of the copending claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 1-3, 6, 7, 10-15, 18-27, 34-40, 43, 59, and 63 are directed to an invention not patentably distinct from claims 38-43 45 and 46 of commonly assigned USSN 11/483,378; and claims 1, 2, 10-13, 18-25, 34-38, and 59 are directed to an invention not patentably distinct from claims 1-12 of commonly assigned USSN 11/124,620, and claims 1-19 of the commonly assigned USSN 11/396,495 for reasons stated above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned USSNs 11/483,378, 11/396,495, and 11/124,620, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun Crowder whose telephone number is (571) 272-8142. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

PHILLIP GAMBEL, PH.D TD
PRIMARY EXAMINER
TC1600
7/20/06

Chun Crowder, Ph.D.
Patent Examiner
July 18, 2006